

REMARKS

Status of Claims

Claims 1 and 3-15 are pending in this application. Claims 3-15 are withdrawn from consideration as being directed to non-elected subject matter. Claim 1 has been amended to more particularly point out and distinctly claim that which the applicants regard as their invention. Support for the claim amendment can be found, *inter alia*, in cancelled claim 2. No new matter has been added by the present amendment.

Claim Rejections under 35 U.S.C. §102

The rejection of claim 1 under 35 U.S.C. §102(b) as being anticipated by Woo et al., *Pharmaceutical Research*, vol. 18, no. 11, November 2001) is respectfully traversed.

Claim 1 has been amended to incorporate the subject matter of cancelled dependent claim 2. The cited reference does not disclose the use of microspheres with the presently claimed compounds. Accordingly, reconsideration and withdrawal of the rejection is respectfully requested.

Claim Rejections under 35 U.S.C. §103

The rejection of claims 1 and 2 under 35 U.S.C. §103(a) over the combined disclosure of Woo et al. and Filvaroff et al. (US 2002/0058614) is respectfully traversed.

As noted, claim 1 is amended herein to recite the biologically active compounds of claim 2. The Office states that Woo does not disclose the composite microspheres with the peptides of claim 2, but that PLGA microspheres as used to carry insulin are disclosed in Filvaroff. Applicants submit that Filvaroff combined with Woo does not disclose the subject matter of amended claim 1, as the combination of the two references do not teach that the composite

microspheres of the present invention could be used as successful delivery vehicles for the polypeptides set forth in claim 1, including insulin.

Woo merely discloses attempts to prepare composite microspheres for devliery of of bovine serum albumin and horseradish peroxidase, and does not provide any teaching on how to prepare microsphere containing any other active ingredient, or disclose if the composition microspheres containing any other active ingredient could be succesful as a delivery device. For example, insulin is not readily soluble in an aqueous buffer, and so 30% acetic acid is used to prepare the insulin solution (see Example 3, at page 21 of the present specification). This important detail is not taught in Woo.

Filvaroff does not remedy the deficiencies of Woo, as Filvaroff fails to provide one of skill in the art with the motivation or expectation of success to combine the teachings of Woo and Filvaroff together. Filvaroff discloses methods for the treatment and repair of cartilage, including insulin loaded PLGA microspheres. However, Filvaroff notes that the contemplated microspheres are formed by the microencapsulation of the active ingredient in a PLGA matrix. (See Filvaroff, [0196]). The structural differences between composite microspheres and those of Filvaroff are such that one of skill in the art would not expect that a microsphere would work in the same fashion as a composite microsphere.

As noted in the present specification, PLGA microspheres (such as those seen in Filvaroff) are known to have many problems with delivery, including structural or conformational changes of proteins during microsphere manufacturing, storage and release (See Cleland et al., Pharm. Res., 14: 420-5 (1997); and Crotts et al., J. Microencapsul., 15: 699-713 (1998)). As also noted in the specification, PLGA microspheres are also known to have an inconsistent release profile. For example, a high initial burst effect within 24 hours followed by a plateau and then culminating in incomplete release is often seen. (See present specification, pages 2-3.

Composite microspheres (as comprising poly(D,L-lactide-co-glycolide) (PLGA) and poly(acryloyl hydroxyethyl starch) (AcHES) address these problems associated with PLGA microspheres by providing a more stable release profile for the active ingredient and reducing and eliminating degradation and structural integrity changes in the active ingredient. Because of the structural differences in the composite microspheres compared to those set forth in Filvaroff, which result in these important functional differences, one of ordinary skill in the art would not have an expectation that a standard PLGA microsphere could be used as in the same way as the composite microspheres of the present invention. Thus, they would not have an expectation of success combining the teachings of Woo and Filvaroff.

Furthermore, Filvaroff, like Woo, does not disclose how to prepare microspheres for the presently claimed active ingredients. As noted above, insulin is not readily soluble in an aqueous buffer, and so 30% acetic acid is used to prepare the insulin solution, which is not disclosed in Filvaroff.

Accordingly, Applicants respectfully request that these rejections be withdrawn.

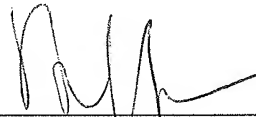
Conclusion

In view of the foregoing amendments and remarks, the application is respectfully submitted to be in condition for allowance, and prompt, favorable action thereon is earnestly solicited.

If there are any questions regarding this amendment or the application in general, a telephone call to the undersigned would be appreciated since this should expedite the prosecution of the application for all concerned.

If necessary to effect a timely response, this paper should be considered as a petition for an Extension of Time sufficient to effect a timely response, and please charge any deficiency in fees or credit any overpayments to Deposit Account No. 05-1323, Docket No. 104072.B870248.

Respectfully submitted,



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